Remarks

Claims 48 to 76 are pending in this application. Claim 69 is withdrawn, claims 70 to 76 have been added. Claims 48 and 57 have been amended to introduce the wording of the preamble into the body of the claim. Claim 63 has been amended to introduce a reference to the CUP1 promoter. Support for this amendment can be found on, e.g., page 26, line 29, page 27, line 17 and page 28, line 1 and so on. Claim 66 has been amended to introduce the word episomal before "propagation" in (d). Support for this amendment can be found throughout the specification, e.g., on page 11, line 20 or page 13, line 26. The amendments to claim 68 and support therefore as well as new claim 70 are discussed below. Support for new claims 71 to 73 is provided starting on page 22 in the discussion entitled "Bait vector", e.g., on page 28, lines 14 and 15 and lines 28 and 29. Similarly, support for new claim 74 can be found, e.g., on page 31, line 1; support for new claims 75 and 76 can be found, e.g., on page 23, lines 14 and 15.

Election

On page 2, the Office confirms applicants election of group I. The Office identifies claims 48 to 68 as the claims under examination.

Priority

On page 2, the Office expressed the opinion that the specification as filed in the U.S. does not correspond to the original international application.

New counsel for applicants has carefully reviewed the paper records as well as the electronic file available on the USPTO website.

From this review, it appears that this application was filed on March 28, 2003 as international application no. PCT/EP03/03287. The U.S. national phase was initiated on September 28, 2004 indicating that an copy of the international application as filed was communicated by the International Bureau. However, applicants submitted an extra copy of the publication of international application no. PCT/EP03/03287 (W03/083136) as a backup.

At the time of initiating the national stage, a preliminary amendment was filed canceling claims 1 to 47 and adding new claims 48 to 69. Being filed after the U.S. filing date of the application, the preliminary amendment was not part of the original disclosure.

In view of this, the undersigned believes that the application was correctly identified as a U.S. national stage application of international application no. PCT/EP03/03287.

However, the Office is urged to contact the undersigned at the number provided below to discuss this matter further in case the undersigned, having not been involved in the original filing, was not able to fully appreciate the source of the Office's concern.

Oath/Declaration

The Office expressed the opinion that the application presents a claim for subject matter not originally claimed or embraced in the statement of the invention. In particular, the Office stated that the new matter is claim 68 and request a new oath or declaration under 37 CFR §1.67.

A oath was submitted on December 22, 2004 identifying the application as an U.S. national stage of international application no. PCT/EP03/03287, filed March 28, 2003. Claim 68 was submitted in a preliminary amendment submitted on September 28, 2004 subsequent to the original filing. Applicants have amended claim 68 to address the Office's new matter concerns. In view of this, it is believed that no supplemental oath or declaration is required.

Specification

On page 3, the Office requested that applicants insert Sequence Identifiers into the specification where appropriate.

Applicants have inserted Sequence Identifiers to address the Office's concern.

Claim Objection

On page 3, the Office objected to claims 66 and 67 as being dependent from cancelled claim 1.

In response, applicants have amended the claims to depend from claim 48. Applicants would like to thank the Office for noting this informality.

Written Description

On pages 3 to 6, the Office rejected claims 48 to 65 and 68 under 35 USC §112, first paragraph, as containing subject matter which was not described in the specification as to reasonably convey to one skilled in the relevant art that the inventors had, at the time of filing, possession of the claimed invention.

The Office's rejection focused in particular on the terminology "parts thereof" which is used in the claims in context of, e.g., a "first membrane bound protein" and "second protein", e.g., first membrane bound protein or parts thereof. At the bottom of page 4, the Office stated that the specification "does not teach how to screen for parts of proteins that will interact" and further "[the specification] does not describe using a fragment of a protein that is very short in length such as one amino acid."

Applicants would like to direct the Office's attention to page 10, first paragraph of the specification. Here the specification explains, in the context of "first membrane bound protein or part thereof" that "any **part** of such protein can be used as long as it is capable of being attached to the membrane and capable of interacting with the second protein strongly enough so that split-ubiquitin is formed." In the context of "second protein or part thereof," the specification explains that "a part of such protein is sufficient as long as it is capable of interacting with the first membrane bound protein or part thereof, strong enough that split-ubiquitin is formed."

Applicants submit that the knowledge in the art as to produce parts of proteins is high. For example, well known proteolytic digestion can be used to create parts of a protein. Parts of proteins that meet the above stated definition can be readily ascertained. In fact, the method described in the present application can be readily adapted to identify such parts:

Assuming a full length first membrane protein, e.g., a full length receptor, is used to identify a second protein, e.g. another, second, membrane protein. After this second protein has been identified, it could be used to identify which parts of the first membrane protein (e.g., single domains, transmembrane domains or fragments comprising multiple membrane domains of the receptor protein) would still be capable of interacting with the second protein. Whether this part of the first membrane molecule was still capable of being attached to membrane could be identified by extracting the membrane fraction of the cell expressing the first membrane molecule or its parts. Methods for selectively extracting the membrane fraction of a cell are well known and have been used for decades in life science research (see for example, Molloy *et al.* (1989) *Electrophoresis* **19**(5):837-844 and David *et al.* (1997) *J. Biol. Chem.* **272**:15553-15561).

The disclosure also describes the screening of libraries to identify the second protein. Library construction is described starting on page 41 of the specification. Individual clones of such libraries will, by their very nature, also contain less than full length proteins, ergo

parts of the second protein. Those parts of the second protein that are capable of interacting with the "first membrane bound protein" as set forth in the definition of the term will be selected via the method of, e.g., claim 48. Thus, the specification does teach how to screen for parts of proteins that will interact (Compare bottom of page 4 of the Office Action – However, other methods known in the art would also be available to identify the relevant parts, such as the method described by Stagljar (PNAS 95:5187-92) as further discussed below).

Applicants also respectfully submit that information which is well known in the art need not be described in detail in the specification. See, e.g., MPEP §2163(II)(A)(2) and *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986). See also MPEP §2163 (II)(3)(a) and its reference to *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1085 (Fed. Cir. 2005) ("The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge). There is a strong presumption that the written description requirement is fulfilled by original claims. See *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (MPEP §2163 (I) (A)). Applicants submit that *In re Wertheim* is applicable here since the rejected language was part of the original claims.

At the bottom of page 5, the Office rejected claim 68 also under 35 USC §112, first paragraph. The Office expressed the opinion that there is no disclosure in the specification for pharmaceutically active agents that interfere with protein-protein interactions. The Office acknowledges that there is disclosure of small compounds that block protein-protein interactions.

In the next paragraph on page 6, the Office rejected claim 68 under 35 USC §112, second paragraph, as being indefinite. In particular, the Office expressed the opinion that it is unclear what properties make the agent potentially pharmaceutically active.

Applicants have amended claim 68 to refer to "compounds" and added claim 70 which refers to "pharmaceutical drugs." Applicants have also eliminated the term "potentially" as rejected by the Office. Support for the amendments to claim 68 can be found on page 4 of the disclosure, in the paragraph starting on line 7. Support for the term pharmaceutical drug (new claim 70) can be found in original claim 46.

35 USC §102(b) Rejection

On pages 6 and 7, the Office rejected claims 48 to 65 under 35 USC §102(b) in view of Stagljar et al. (PNAS 95:5187-92, in particular p. 5187, 5191 and Fig. 2; hereinafter "Stagljar"). The Office expressed the opinion that every element of the claims is disclosed by this reference.

Stagljar discloses a genetic system based on split-ubiquitin for the analysis of interactions between membrane proteins *in vivo*. Stagljar is discussed in the background section of the present application (page 3) and some differences relative to embodiments of the present invention are discussed in the subsequent paragraph.

However, in addition, applicants have amended the claims to clarify that the bait and the prey vectors are maintained episomally. In contrast, Stagljar's bait construct is integrated into the yeast genome (see, e.g., discussion on page 5189, left column ("The resulting fusion genes were integrated . . .") (Episomally maintained prey vectors are shown by Stagljar, e.g., in Fig. 5). An episomally maintained bait vector offers more flexibility with respect to what "bait protein" can be used (e.g., proteins other than yeast proteins) and also provides considerable time cutting advantages since it eliminates, e.g., the need of integrating every protein tested. Furthermore, the episomal maintenance of the bait vector offers the possibility to control the expression levels, leading to a more reliable output of the methods, kits and vectors as presently claimed than those provided by Stagljar's system. Furthermore, Stagljar's system having an integrating bait vector, apart from being somewhat difficult to handle, is only suitable for yeast proteins, but not for proteins from other species, e.g., mammalian proteins.

Claim 48 now requires:

> "(d) . . . wherein both the bait vector and the prey vector are maintained episomally." (emphasis added)

Claim 57 has been amended similarly.

Claim 48 also requires:

> "introducing the bait vector and the prey vector into the host cell such that an interaction between the expressed first and second proteins and/or their parts can take place, . . . which . . . in turn leads to activation of an intracellular protease and proteolytic separation of the transcriptional activator" (emphasis

added)

Bürki, 2001 (see Information Disclosure Statement of July 6, 2007), who tested a bait construct in an episomal CEN/ARS vector with a strong ADH1 promoter did not observe such an interaction leading to proteolytic separation of the transcriptional activator as set forth in, e.g., claim 48. Rather, in her experiments the bait construct was self-activating, leading to false positives throughout (see also page 23, para. (4) of the specification). Explanations of the phenomenon of self-activation vary. One explanation is that it is a result of a cellular response to the bait, which results in its removal from the membrane, followed by its degradation, which in turn results in the release of the transcriptional activator (See, e.g., Schroeder, Mol. Biotechnol. 34(2):279-90 (2006), not attached, but can be provided upon request). Such self-activation will not allow:

> "detecting said interaction between said first membrane bound protein or part thereof and said second protein or part thereof" (emphasis added)

as required by claim 48 as amended. See claim 57 which contains similar language.

In view of this self-activation, Bürki's bait construct proved to be unsuitable for use, e. g., in a screening system based on such detection. However, considering that, e.g., the disclosure of WO 02/27020 (Inventors : Stagljar et al.; see Information Disclosure Statement of September 28, 2004) on page 16 explicitly states that it is "advisable to use integrative vectors", it appears that the outcome of her experiments would not have struck the person skilled in the art as surprising. Bürki's previous attempts to put her bait construct under a weak promoter (Wbp 1 promoter) in the context of an integrating vector had failed (no interaction between bait first protein sequence and the second protein sequence could be observed), providing also little incentive to try, alternatively, weak promoters in context of episomal vectors (see, e.g., claims 64, 75 and 76).

Applicants have shown above that a written description has been provided for all pending claims which have not been withdrawn. Applicants have also shown that claim 68, as amended, does not contain new matter. Finally, applicants have shown that the pending claims are patentable over "Stagljar."

In view of the above, an early allowance of this case is respectfully requested.

No fee in addition to those submitted herewith is believed to be due. However, any petition required for consideration of this paper is respectfully requested herewith and the Commissioner is authorized to charge deposit account 50-3135 for fees that might be required for such consideration.

Respectfully submitted,

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